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Unbalanced Translocation in a Mother and Her Son in One of Two 5;10 Translocation Families

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We present two families with different distal long arm 5;10 translocations. In one family the propositus and his mother inherited the same derived chromosome 10 from the maternal grandfather who has a balanced t(5;10)(q35.3;q26.13). The phenotype of both the affected patients is milder and only partially overlaps with that of previous cases of distal 10q deletion. Other previously reported cases of transmitted imbalance are also remarkable for mild phenotype, occurrence of deletions rather than duplications and a strong bias toward maternal as opposed to paternal transmission.

In the second family, the propositus inherited a derived chromosome 10 from his mother who carries a balanced t(5;10)(q35.1;q26.3) translocation; his clinical manifestations are consistent with an emerging phenotype for distal 5q duplications.

KEY WORDS: familial chromosome imbalance, unbalanced translocation, duplication 5q, deletion 10q, chromosome painting

INTRODUCTION

Imbalances of the distal long arm of chromosome 10 are uncommon but claimed to cause a distinct phenotype [Wulfsberg et al., 1989] and imbalances of the distal long arm of chromosome 5 are rare [Lai et al., 1992]. Here we compare the phenotypic findings in patients with imbalances of these regions from two families with those previously reported. In addition, our first family includes an unusual case of a balanced grandparental translocation carrier having a chromosomally unbalanced daughter who in turn had a chromosomally unbalanced son.

MATERIALS AND METHODS

GTL-banded chromosomes were prepared by standard methods after semisynchronisation of cultures with FdU and release with thymidine [Webber and Garson, 1983]. Chromosome painting with a whole chromosome paint for chromosome 5 (Cambio, Cambridge, UK) was performed by a modification of the method of Pinkel et al. [1988].

CLINICAL REPORTS

Family 1

Following a normal pregnancy and delivery, the propositus (III-1, Fig. 1) was referred because minor anomalies were noted at birth. His birth weight was 3.5 kg. At 6 weeks his weight was 3.7 kg (3rd centile) and head circumference (OFC) was 37.3 cm (10th centile). He had plagiocephaly, torticollis, a high forehead with bitemporal narrowing, prominent supraorbital ridges, deep-set eyes, prominent and broad nasal bridge, thin upper lip and micrognathia (Fig. 2), long fingers and broad thumbs. Feet and skin were normal. He had a long glubal cleft. He was hypotonic and developmentally delayed. Testes were palpable in the inguinal canal. He had been investigated for a urinary tract infection and found to have bilateral hydronephrosis and a thick walled bladder. Serum calcium and parathormone levels were normal.

His mother (II-2), to whom he bore a remarkable resemblance (Fig. 3), lived in sheltered accommodation and was mildly developmentally delayed. She did not walk until age 3 years. She had attended special schools. A normal karyotype had been reported in 1979 when she was 7 years old.

On examination at the age of 20 years, her height was 1.7 m and she was microcephalic (OFC = 51.2 cm $\ll$3rd centile). She had deep-set eyes with apparent hypertelorism, prominent supraorbital ridges, upslanting eyebrows, broad nose, prominent nasal bridge,

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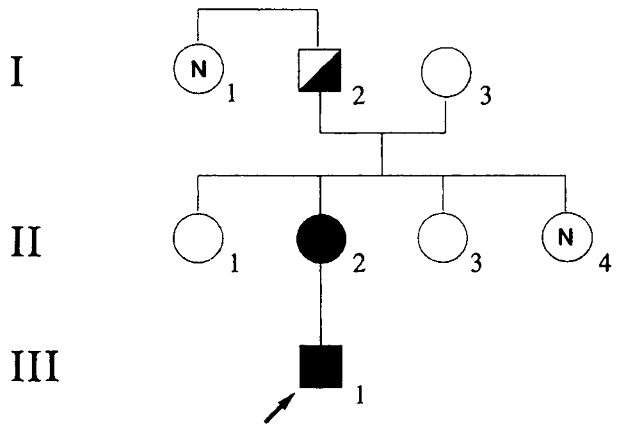

Fig. 1. Pedigree of family 1. Full shading indicates affected unbalanced translocation individuals, and half-shading the normal carrier.

large jaw, and broad thumbs with otherwise normal hands and feet. She had much difficulty with incontinence and detrusor instability and had required an ileocystoplasty. Investigations had shown a small thick walled bladder with no hydronephrosis.

Family 2

The propositus (IV-1 in Fig. 4) was the first child of healthy 22-year-old parents. A forceps delivery was carried out at 38 weeks following induction of labour for fetal distress. Birth weight was 2.2 kg (<3rd centile) and OFC 32 cm (<3rd centile). He was discharged in good condition at 5 days, but at 3 weeks he became floppy and uninterested in feeds. He was admitted to hospital where he was found to have a supraventricular tachycardia leading to circulatory failure. A small ventricular septal defect was found. He was treated successfully with amiodarone. Serum calcium was only 1.4 mmol/litre and his magnesium level was also reduced at 0.5 mmol/litre. He was treated with intravenous calcium and magnesium supplements. Plasma parathormone level was normal, and a thymic shadow was present in the chest film. During this illness the child also developed seizures and abnormal movements, plus candidiasis of the mouth and skin flexures.

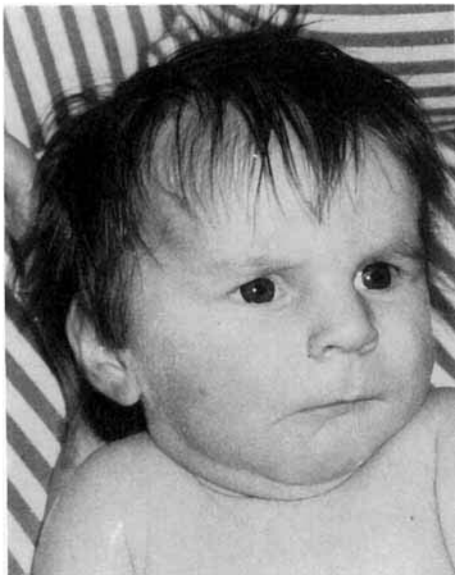

Fig. 2. The propositus (III-1) of family 2 at the age of 3 months. Note the deep-set eyes, prominent nasal bridge and micrognathia.

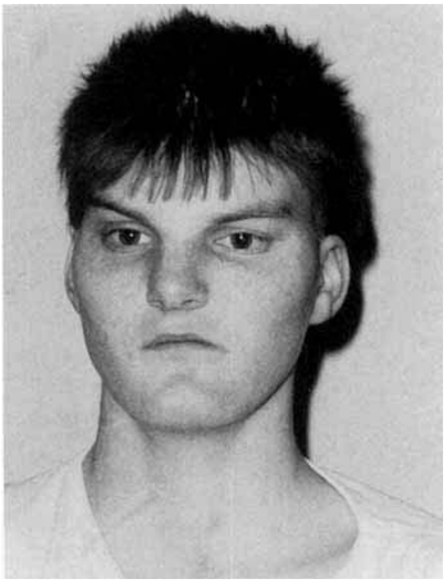

Fig. 3. The mother (II-2) of the propositus of family 2 at the age of 20. Note the deep-set eyes, and prominent nasal bridge.

The patient was reexamined at the age of 9 years (Fig. 5). He had recently begun to have grand mal seizures, and serum calcium, which had previously returned to normal, was again low. Plasma parathormone, although within normal limits (1.4 pmol/l), was thought to be inappropriately low considering the degree of hypocalcemia. He had severe developmental delay but was pleasant and sociable. Height and weight were below the 3rd centile, and OFC was approximately 4 standard deviations below the mean for his age. He had a round face with a long hypoplastic philtrum, small mouth with thin upper lip, downward slanting palpebral fissures, anteverted nares, posteriorly angulated ears and irregularly positioned lower teeth. Shortly after we saw him, the child was placed on a gluten-free diet for a suspected diagnosis of coeliac disease. Although no mucosal biopsy was carried out to confirm this, his well-being immediately improved as did his previously loose, frequent stools and growth rate.

The patient's maternal grandmother (II-7), who must have been a translocation carrier, died at the age of 40 of subarachnoid haemorrhage. Her mother and brother (I-2 and II-4) also died of subarachnoid haemorrhage in their 40s. Her deceased sister (II-5) and 2 nephews (III-1 and -2) were mentally handicapped. Cerebral angiography in the patient's mother (III-5) and a CT scan in the patient's brother (IV-3) showed tortuosity of the cerebral arteries in both, but no aneurysms.

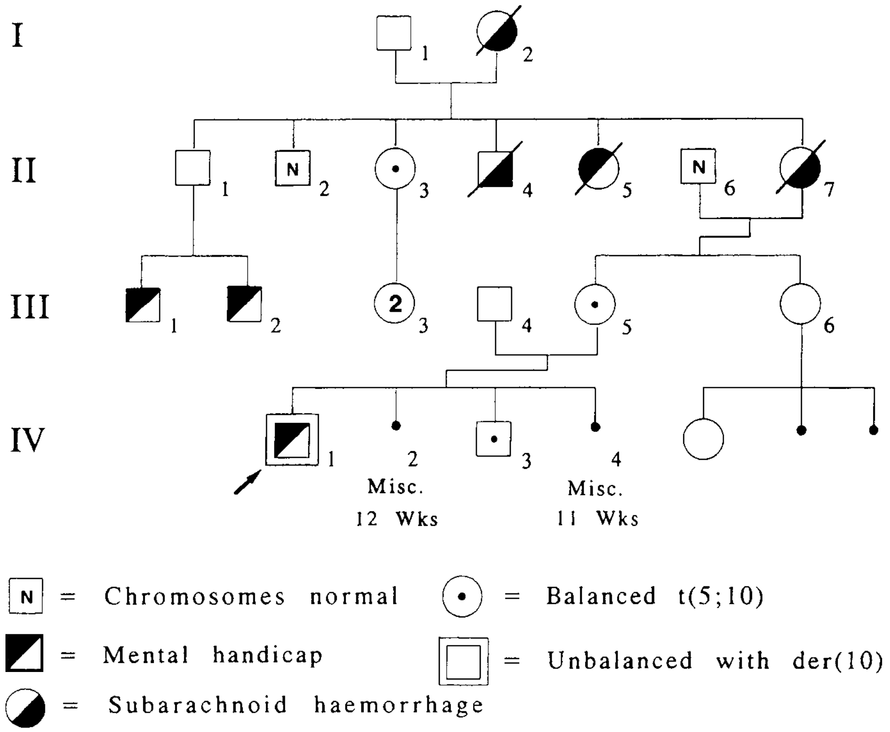

Fig. 4. Pedigree of family 2.

CYTOGENETIC AND MOLECULAR CYTOGENETIC FINDINGS

Family 1

An abnormality of chromosome 10 was identified neonatally in the propositus and subsequently in his phenotypically abnormal mother (Fig. 6). However, in the phenotypically normal grandfather, a balanced translocation 46,XY,t(5;10)(q35.3;q26.13) (Fig. 6) was detected and the unbalanced karyotypes of his daughter and grandson were therefore interpreted as 46,XX or XY,−10,+der(10)t(5;10)(q35.3;q26.13)pat or mat. Cell lines from the proband (III-1), his mother (II-2),

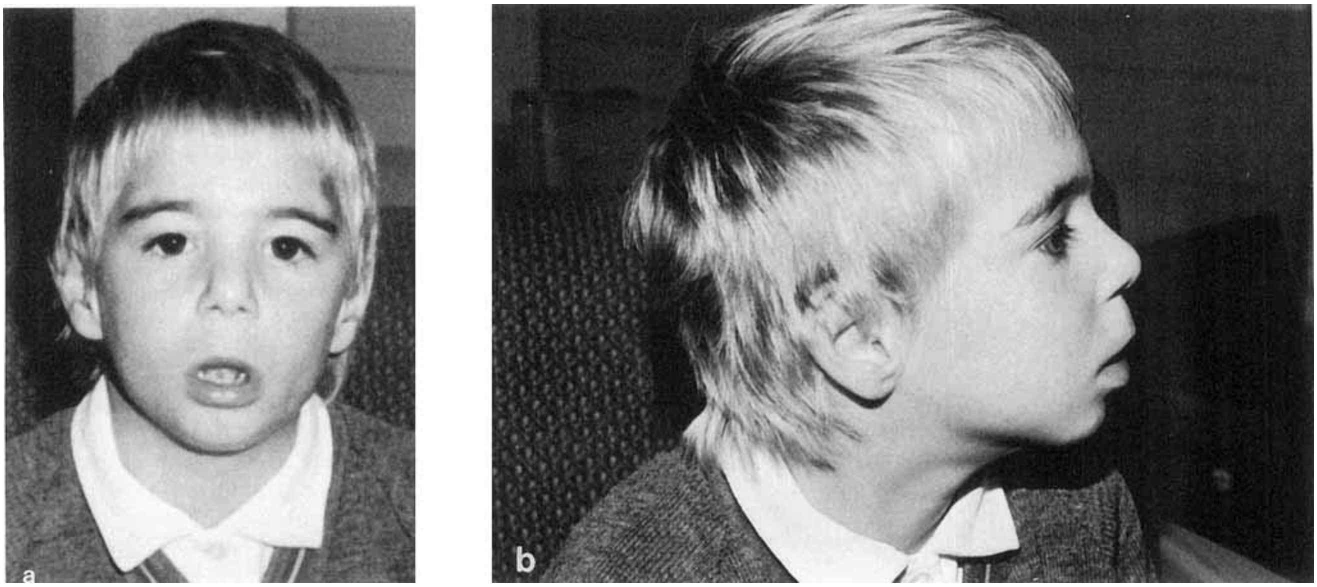

Fig. 5. **a, b:** Frontal and lateral views of the proband (IV-1) of family 1 at the age of 9 years.

and his grandfather (I-2) have been established at the European Collection of Animal Cell Cultures (refs. DD734, DD272, and DD816, respectively).

Family 2

An abnormality of chromosome 10 was detected when the propositus was age 8 (Fig. 6). A balanced t(5;10)(q35.1;q26.3) translocation was found in his phenotypically normal mother and brother (Fig. 6); the propositus' unbalanced karyotype was therefore 46,XY,−10,+der(10)t(5;10)(q35.1;q26.3)mat. His maternal great aunt (II-3) was also found to carry the balanced (5;10) translocation, but it has not yet been possible to test other relatives including those with mental handicap. A cell line from the balanced translocation carrier (IV-3) has been established at the European Collection of Animal Cell Cultures (ref. DD766).

As the relative difference in size between derived and normal chromosomes 10 was similar in both families (Fig. 6) it was suggested, before the balanced 5;10 was discovered in the grandfather of family 1, that they might each have segregated from a balanced translocation common to both families. However, by hybridizing to the derived 10 in family 1 and failing to hybridize to the derived 10 in family 2, the chromosome 5 library was alone sufficient to distinguish between the two derived chromosomes 10 (Fig. 6). In addition, chromosome painting could not directly demonstrate the reciprocal tips of chromosomes 5 and 10 in either translocation in its balanced form, suggesting that imbalances for these are beneath the detection level of the method which is currently thought to be about 2.5 megabases [Gould et al., 1992].

DISCUSSION

In these two families, both translocations involve distal segments of the long arms of chromosomes 5 and 10 and, in each case, the affected individuals inherited a derived chromosome 10.

In Table I the del(10q) column is based on 18 patients reviewed by Wulfsberg et al. [1989] and 10/18 (together with our own patients), had deletions distal to 10q26 and were relatively mildly affected. The other 8/18 with deletions extending into 10q25 were more likely to have had anal and genital anomalies and not to have survived. In family 1, the deletion of chromosome 10 is cytogenetically larger than the duplication of chromosome 5 which could not be detected using the chromosome 5 paint. Nevertheless, the prominent nasal bridge and thin upper lip seen in propositus and mother are characteristic of 5q duplication rather than 10q deletion, and other findings, with the exception of the broad beaked nose in the mother and undescended testes in the son, are common to patients with both kinds of imbalance. All males with distal 10q deletions appear to have had undescended testes or ambiguous genitalia, suggesting that a locus involved in male sexual differentiation may map to this region [Wilkie et al., 1993].

Several manifestations associated with distal 10q deletions by Wulfsberg et al. [1989] were not seen in the patients of our family 1 including large or malformed ears, a short or webbed neck, microphthalmia, syndactyly of the fingers or toes, hammer toe, club foot, or an anal abnormality. Unlike the 12 survivors reviewed by Wulfsberg et al. [1989], they had only moderate mental impairment. Conversely, urinary tract abnormalities and broad thumbs are found in both family 1

TABLE I. Summary of Phenotypic Findings in Both Families

	del(10q)[a]	Family 1		Family 2	dup(5q)
	n = 18	Child	Mother	Child	n = 9
Low birth weight	7/18	−	−	+	2/2
Low head circumference at birth	−	−	−	+	2/2
Postnatal growth defect	9/12	N/A[c]	−	+	8/8
Downward slant to palpebral fissures	6/18	−	−	+	5/6[d]
Postnatal microcephaly	12/18	N/A	+	+	5/8
Strabismus	8/12	−	−	−	5/9
Hypertelorism	8/18	−	+	+	5/5[d]
Prominent nasal bridge	−	+	+	+	8/8[d]
Thin upper lip	−	+	+	+	8/9
Low set/abnormal ears	−	−	−	+	5/5[d]
Long philtrum	−	−	−	+	6/9[d]
Small mouth	−	−	−	+	2/3[d]
Ventricular septal defect	7/18[b]	−	−	+	4/9
Cardiac conduction defects	−	−	−	+	3/7
Seizures	−	−	−	+	1/5
Broad/beaked nose	16/18	+	+	−	−

[a]The denominator given for each finding is the number of cases on which a judgment can be made from the published reports on the presence or absence of that finding.
[b]Nine patients had congenital heart disease, among which seven had a ventricular septal defect either alone or combined with other defects.
[c]N/A, not applicable.
[d]Based in part on our interpretation of published photographs.

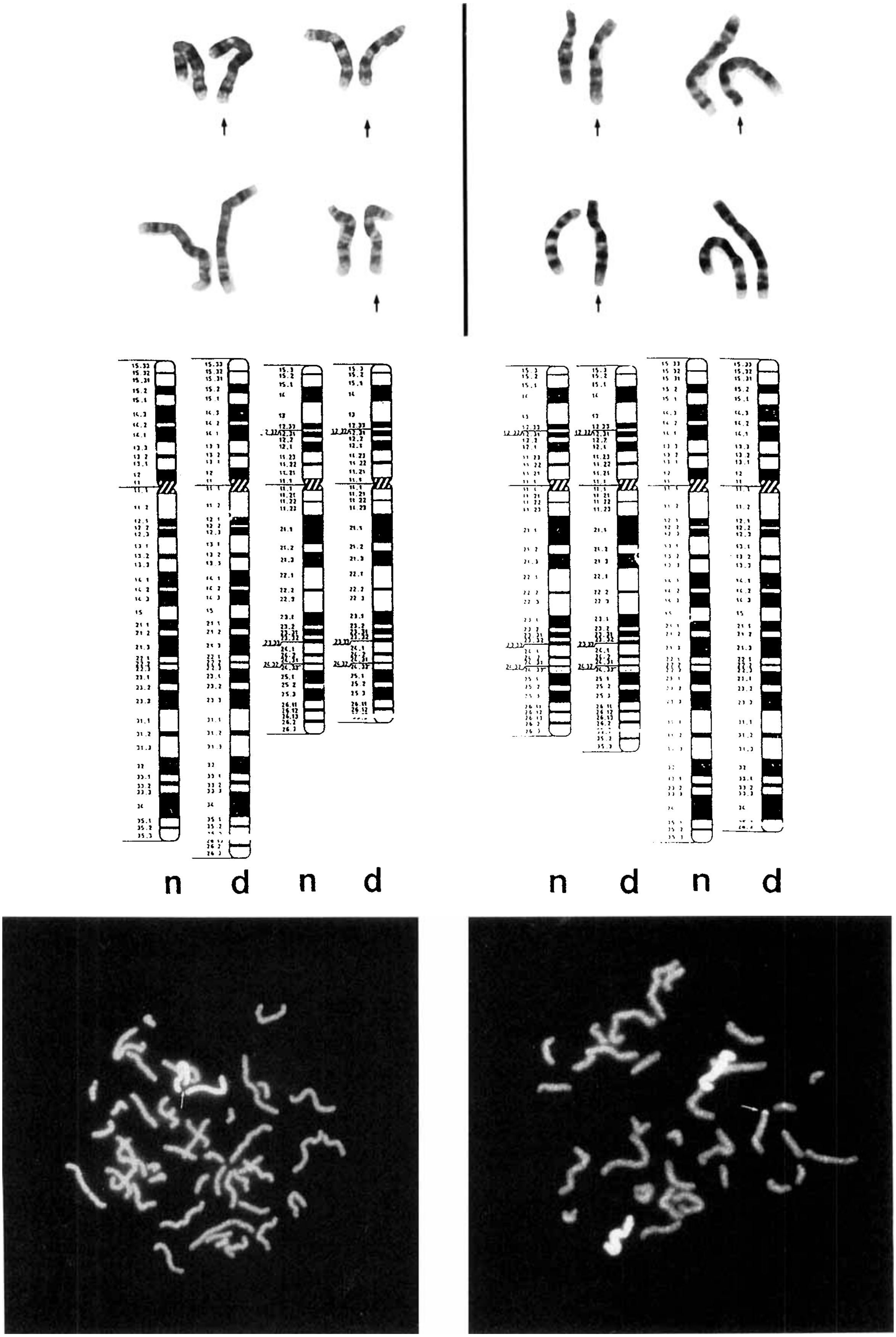
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TABLE II. Heritable Euploid Autosomal Imbalances in Phenotypically Affected Parents and Children

Chromosome	Type of imbalance	Extent	Parent	Reference
1	duplication	q25→q25	mother	van Dyke [1988]
3	deletion	p25→pter	mother	Tazelaar et al. [1991]
4	duplication	q31.22→q33	mother	van Dyke [1988]
4	deletion	q33→q35.1	mother	Curtis et al. [1989]
4	deletion	q33→qter	mother	Herzog et al. [1993]
4 or 14	deletion[b]	11 megabases[a]	father	Cooke et al. [1989]
5	deletion	p15.32→pter	mother	Baccichetti et al. [1988]
5	deletion	p15.1→pter	mother	Kushnick et al. [1984]
5	deletion	p13→p15.1	mother	Walker et al. [1984]
8	deletion	p23.1→pter	father	Pettinatti et al. [1992]
9	deletion	q13.3	mother[c]	Magenis et al. [1989]
10	deletion[b]	q26.13→qter	mother	Present family 2
11	deletion	q24.2	mother	Neavel and Soukup [1994]
13	deletion	q14.1→q21.3	mother	Fukushima et al. [1987]
15	duplication	q11→q13	mother	van Dyke [1988]
18	deletion	q22.3→qter	mother	Miller et al. [1990]
20	deletion	p11.2→p12.2	mother	Anad et al. [1990]
21	deletion	q11→q21.3	mother	Roland et al. [1990]
22	deletion	q11.21→q11.23	mother	Wilson et al. [1991]

[a]Extent of deletion determined by Fluorescence Activated Cell Sorter.
[b]Deletion associated with translocation.
[c]Mother mosaic for deletion.

patients and have not been reported in either del 10q or dup 5q patients.

The dup 5q column in Table I is based on nine patients with duplications distal to 5q33 [Zabel et al., 1978; Curry et al., 1979; Passarge et al., 1982; Kumar et al., 1987]; all have concomitant deletions arising from the segregation or recombination of balanced parental rearrangements. Nevertheless, the affected individual from family 2 whose duplication of chromosome 5 is cytogenetically larger than his deletion of chromosome 10 had 14 of the traits previously recorded in dup(5q) patients although 6 of these are also found in patients with 10q deletion (Table I).

Hypocalcemia was found in our patient although it was not clear whether this was the result of hypoparathyroidism or some other metabolic cause. Hypocalcemia was reported in another patient with a duplication of distal 5q by Lai et al. [1992] but was more likely to have been the result of the concomitant deletion of 10p found in their patient which has already been associated with many of the findings of DiGeorge syndrome including hypoparathyroid hypocalcemia.

We are not aware of another family comparable to family 1 in which the unbalanced offspring of a balanced translocation carrier has gone on to have a child with the same imbalance. Nevertheless, Table II includes 18 previous families in which an affected parent with an unbalanced karyotype has transmitted the same imbalance to one or more affected children but excludes families with inherited numerical abnormalities or supernumerary marker chromosomes. In addition, 24 families with stable transmission of autosomal ring chromosomes which include cases with proterminal deletions have also been reported [Kosztolányi et al., 1991; Falik-Borenstein et al., 1992].

Sixteen of nineteen families in Table II have deletions and 3/19 have duplications. This is surprising in view of the generally greater severity of phenotypic effects resulting from deletion as opposed to duplication but may reflect the fact that deletion is a more common chromosomal mutation than duplication. Evidently these imbalances are compatible with fertility and most authors comment on the mildness of the phenotypic effects found.

There is a strong bias towards maternal transmission of the unbalanced karyotypes with only 2/19 transmitted by fathers and 17/19 by mothers. A similar bias is found among the familial ring chromosomes where 2/24 were paternally transmitted and 22/24 maternally [Kosztolányi et al., 1991; Falik-Borenstein et al., 1992]. This may reflect a bias towards ascertainment of mildly handicapped mothers and their children; mildly handicapped fathers might be less readily named by mothers

Fig. 6. **Upper** panel: Partial karyotypes illustrating the balanced and unbalanced translocations in family 1 (left set) and family 2 (right set) with the derived chromosomes arrowed in each case. **Top left:** The balanced translocation from the grandfather (I-2) of the proband of family 1. **Bottom left:** The unbalanced translocation from the mother (II-2) of the proband of family 1. **Top right:** The balanced 5;10 translocation from the brother (IV-3) of the proband of family 2. **Bottom right:** The unbalanced 5;10 translocation from the proband of family 2 (IV-1). Note the apparent similarity between the derived chromosome 10 in family 1 and the normal chromosome 10 in family 2 and vice versa. **Middle** panel: Idiograms of the balanced forms of the translocations with normal chromosomes marked "**n**" and the derived chromosomes "**d.**" **Left set:** The t(5;10)(q35.3;q26.13) translocation from family 1. **Right set:** The t(5;10)(q35.1;q26.3) translocation from family 2. **Lower** panel: Chromosome painting with the chromosome 5 library. **Left** metaphase: The balanced 5;10 translocation of family 1 in the grandfather (I-1); note the lack of hybridization to any C-group chromosome. The arrowed tip of the derived 5q remained clearly unpainted when viewed under the microscope. **Right** metaphase: The balanced 5;10 translocation of family 2 in the proband's brother (IV-3); note the positive hybridization of the chromosome 5 paint to the arrowed derived chromosome 10.

or less easily traced. Mildly affected mothers may also be more liable to exploitation by normal men than vice versa. Alternatively, the presence of a cytogenetic imbalance may lead to a greater impairment of male as opposed to female gametogenesis as has already been proposed in ring chromosome carriers [Kosztolányi et al., 1991] and, as a result of chromosome pairing failure, in balanced translocation carriers [Chandley, 1988]. Any role for imprinting seems unlikely as only two of the unbalanced segments in Table II [Magenis et al., 1989; Wilson et al., 1991] are contained within segments which share homology with regions which are subject to imprinting in the mouse [Hall, 1990].

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REFERENCES

Anad F, Burn J, Matthews D, Cross I, Davison BCC, Mueller R, Sands M, Lillington DM, Eastham E (1990): Alagille syndrome and deletion of 20p. J Med Genet 27:729–737.

Baccichetti C, Lenzini E, Artifoni L, Caufin D, Marangoni P (1988): Terminal deletion of the short arm of chromosome 5. Clin Genet 34:219–223.

Chandley AC (1988): Meiotic studies and fertility in human translocation carriers. In Liss AR (ed): "The Cytogenetics of Mammalian Autosomal Rearrangements." New York: Alan R Liss, pp 361–382.

Cooke A, Tolmie JL, Colgan JM, Greig CM, Connor JM (1989): Detection of an unbalanced translocation (4;14) in a mildly retarded father and son by flow cytometry. Hum Genet 83:83–87.

Curry CJR, Loughman WD, Franke U (1979): Partial trisomy for the distal long arm of chromosome 5 (region q34-qter). A new clinically recognizable syndrome. Clin Genet 15:454–461.

Curtis MA, Smith RA, Sibert J, Hughes HE (1989): Interstitial deletion, del(4)(q33q35.1) in a mother and two children. J Med Genet 26:652–654.

Falik-Borenstein TC, Pribyl TM, Pulst SM, Van Dyke DL, Weiss L, Chu ML, Kraus J, Marshak D, Korenberg JR (1992): Stable ring chromosome 21: Molecular and clinical definition of the lesion. Am J Med Genet 42:22–28.

Fukushima Y, Kuroki Y, Ito T, Kondo I, Nishigaki I (1987): Familial retinoblastoma (mother and son) with 13q14 deletion. Hum Genet 77:104–107.

Gould CP, Waters JJ, Mercer AM, Challinor PR, Hill SM, Johnson RA, Simpson PJ, Delhanty J, Hulten MA (1992): Limitations of whole chromosome fish analysis in clinical cytogenetics: Failure of detection of translocated proterminal segments shorter than 2.5 Mb. Eur Soc Hum Genet Denmark:78, 115 (Abstract).

Hall JG (1990): Genomic imprinting: Review and relevance to human diseases. Amer J Hum Genet 46:857–873.

Herzog R, Babu A, Popescu S, Konstantinovska F, Punales-Morejon D, Kupchik G, Penchaszadeh VB (1993): Chromosome 4 deletion (4q33-4qter) in a mother and son. Am J Hum Genet 53 Suppl. 1573 (Abstract).

Kosztolányi G, Méhes K, Hook EB (1991): Inherited ring chromosomes—an analysis of published cases. Hum Genet 87:320–324.

Kumar D, Heath PR, Blank CE (1987): Clinical manifestations of trisomy 5q. J Med Genet 24:180–184.

Kushnick T, Rao KW, Lamb AN (1984): Familial 5p-syndrome. Clin Genet 24:472–476.

Lai MMR, Scriven PN, Berry AC (1992): Simultaneous partial monosomy 10p and trisomy 5q in a case of hypoparathyroidism. J Med Genet 29:586–588.

Magenis RE, Lahr M, Hafits-Borchardt VA, Lawce H, Wilson T (1989): Inherited microdeletion syndrome, due to loss of single bond 9q31.3: The continuing care for high resolution chromosome studies in unexplained mild mental retardation. Amer J Hum Genet 45 Suppl. A81, 314 (Abstract).

Miller G, Mowrey PN, Hopper KD, Frankel CA, Ladda RL (1990): Neurologic manifestations in 18q-syndrome. Am J Med Genet 37:128–132.

Neavel CB, Soukup S (1994): Deletion of (11)(q24.2) in a mother and daughter with similar phenotypes. Am J Med Genet 53:321–324.

Passarge E, Bartsch-Sandhoff M, Rehder H (1982): Fetal manifestation of a chromosomal disorder: Partial duplication of the long arm of chromosome 5(5q33-qter). Teratology 25:221–225.

Pettenati MJ, Rao N, Johnson C, Hayworth R, Crandall K, Huff O, Thomad IT (1992): Molecular cytogenetic analysis of a familial 8p23.1 deletion associated with minimal dysmorphic features, seizures, and mild mental retardation. Hum Genet 89:602–606.

Pinkel D, Landegent J, Collins C, Fuscoe J, Segraves R, Lucas J, Gray J (1988): Fluorescence in situ hybridization with human chromosome-specific libraries: Detection of trisomy 21 and translocations of chromosome 4. Proc Natl Acad Sci USA 85:9138–9142.

Roland B, Cox DM, Hoar DI, Fowlow SB, Robertson AS (1990): A familial interstitial deletion of the long arm of chromosome 21. Clin Genet 37:423–428.

Tazelaar J, Roberson J, Van Dyke DL, Babu VR, Weiss L (1991): Mother and son with deletion of 3p25-pter. Am J Med Genet 39:130–132.

Van Dyke DL (1988): Isochromosomes and interstitial tandem direct and inverted duplications. In Daniel A (ed): "The Cytogenetics of Mammalian Autosomal Rearrangements." New York: Alan R. Liss, Inc., pp 635–665.

Walker JL, Blank CE, Smith BAM (1984): Interstitial deletion of the short arm of chromosome 5 in a mother and three children. J Med Genet 21:465–467.

Webber LM, Garson M (1983): Fluorodeoxyuridine synchronisation of bone marrow cultures. Cancer Genet Cytogenet 8:123–132.

Wilkie AOM, Campbell FM, Daubeney P, Grant DB, Daniels RJ, Mullarkey M, Affara NA, Fitchett M, Huson SM (1993): Complete and partial sex reversal associated with terminal deletion of 10q: Report of 2 cases and literature review. Am J Med Genet 46: 597–600.

Wilson DI, Cross IE, Goodship JA, Coulthard S, Carey AH, Scambler PJ, Bain HH, Hunter AS, Carter PE, Burn J (1991): DiGeorge syndrome with isolated aortic coarctation and isolated ventricular septal defect in three sibs with a 22q11 deletion of maternal origin. Br Heart J 66:308–312.

Wulfsberg EA, Weaver RP, Cunniff CM, Jones MC, Jones KL (1989): Chromosome 10qter deletion syndrome: A review and report of three new cases. Am J Hum Genet 32:364–367.

Zabel B, Baumann W, Gehler J, Conrad G (1978): Partial trisomy for short and long arm of chromosome 5. J Med Genet 15:143–147.